REMARKS

I. The Specification

Corrected drawings in compliance with 37 CFR § 1.85 are submitted herewith.

The specification is amended herein to merely correct a typographical error; the term "I2R" has been replaced with "III2R". Support for this correction can be found at least at page 35 of the specification which indicates that human heavy chain framework sequences that were used to humanize the 3D1 antibody were from the human subgroup I (see e.g., page 35, lines 13-17). Page 35 of the specification also states that the heavy chain framework sequences were published by Manheimer-Lory, A. *et al.*, J. Exp. Med. 174(6):1639-1652 (1991) (a copy is enclosed with the concurrently filed Information Disclosure Statement). Table I of the Manheimer-Lory reference teaches only two cell lines with the heavy chain variable regions belonging to subtype I: the III2R cell line and the R3.5H5G cell line. It is clear that the use of the term "I2R" rather than "III2R" throughout the specification was a typographical error. Accordingly, the term "I2R" has been replaced with "III2R" at each occurrence. No new matter has been added.

The Examiner has required that the application be reviewed for all spelling, trademarks, and like errors to be corrected. Applicants have made every effort to detect and correct such errors in the specification. Applicants submit that the trademarks known to Applicants are capitalized and the proprietary nature of the marks has been respected.

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II. Status of the Claims

Claims 1-26 are currently pending. Claim 1 has been amended to merely correct an inadvertent typographical error in referring to the cell contacted with the immunoglobulin and to more particularly point out the subject matter that the Applicants regard as the invention. Claims 2 and 3 have been amended to more particularly point out the subject matter that the Applicants regard as the invention. Claim 5 has been withdrawn by the Examiner as directed to a non-elected invention. New claims 6-26 have been added to more particularly point out the subject matter that the Applicants regard as the invention, and all depend from claims currently under examination. Full §112 support for the new and amended claims can be found in the specification on page 2, line 1 to page 8, line 2, page 10, lines 12-14, page 30, lines 10-11, page 31, lines 8-26, and page 38 line 4 to page 39, line 19. No new matter has been added by these amendments.

III. The Rejection Under 35 U.S.C. § 112

Claims 2-3 stand rejected under 35 U.S.C. § 112 second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner contends that the recitation of the terms "modulating" and "treating" is ambiguous. Office Action at page 2. Applicants traverse.

Applicants contend that the term "treating" is not ambiguous. The term treating is described on page 30, lines 5-13 of the specification.

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> Accordingly, the invention encompasses methods for treating the disease, as described herein, comprising administering immunoglobulin(s) that binds B7-1 and/or B7-2. ...The immunoglobulin that binds B7-1 and/or B7-2 can be administered to a person having transplanted tissue, organ or cells. Inhibiting the B7 pathway prevents or reduces the rejection of the transplanted tissue, organ or cell. The invention pertains to treating acute and/or chronic transplant rejection for a prolonged period of time (e.g., days, months, years).

The concept of treating patients with actual or likely rejection of transplanted tissue, organs, and cells is certainly well understood in the art of transplantation. The parameters of transplantation rejection are well defined (e.g. necrosis, inflammation), and treatment is desired to reduce or prevent the symptoms and problems associated with transplantation rejection. However, in order to expedite prosecution Applicants have amended claim 3 to recite "reducing transplantation rejection in a patient", thus obviating the rejection.

Likewise, Applicants contend that the term "modulating" is not ambiguous. The specification teaches as quoted above and on page 30, lines 5-13 that inhibiting the B7 pathway prevents or reduces the rejection of the transplanted tissue organ or cells. The specification also teaches on page 31, line 15-16 "modulating or influencing the B7-2's role can be useful in treating patients with these diseases." Modulating relates to inhibiting the B7 pathway to prevent or reduce rejection of a transplanted organ, tissue or cell. Relying on the teachings of the specification the skilled artisan would understand the metes and bounds of the claimed invention. However, in order to expedite prosecution Applicants have amended claim 2 to recite "inducing immunotolerance in a patient", thus obviating the rejection.

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IV. The Rejection Under 35 U.S.C. § 102(e)

A. Rejection under Freeman *et al.*

Claims 1-4 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Freeman *et al.* (U.S. Patent No. 6,130, 316; hereafter "Freeman"). Office Action at page 3. The Examiner alleges that Freeman teaches the use of B7-2 specific antibodies in order to cause immunosuppression or induce tolerance, including their use to inhibit transplant rejection in various modalities. The Examiner alleges that the antibodies taught by Freeman inherently anticipate the instant claimed invention. Applicants contend that Freeman does not literally or inherently anticipate the instant invention as claimed.

To anticipate the claimed invention, the reference must contain all of the claim limitations. M.P.E.P. § 2131. Claims 1-3 have been amended to recite methods of administering an immunoglobulin to a patient, wherein the immunoglobulin comprises "at least a portion of an immunoglobulin of human origin derived from the III2R and/or the H2F antibody". All other claims depend on claims 1-3 and are thereby encompassed by these amendments. While Freeman discloses that humanized antibodies raised against B7-2 may be humanized and used for immunosuppression (Freeman, column 5, line 63 to column 6, line 16; column 28, line 66 to column 29, line 53), the reference does not disclose that portions of the humanized immunoglobulin can be derived from the I2R and/or the H2F antibody. In addition, claims 1-3, as amended, recite the limitation that the humanized immunoglobulin "has a binding affinity of at least about 10^7 M^{-1}". This limitation is not found in Freeman. Because the claimed invention

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discloses limitations not taught by Freeman, Applicants contend that Freeman can not serve as an anticipatory reference.

Additionally, Freeman did not make any humanized antibodies, but only mentioned humanizing his antibodies in passing (column 28, line 66 to column 29, line 53). In contrast, the antibodies of the present invention are all humanized. In order to serve as an anticipatory reference, Freeman must also enable all aspects of the claimed invention. *Chester v. Miller*, 906 F.2d 1574, 1576-1577, 15 USPQ2d 1336, 1336 (Fed. Cir. 1990). Applicants submit that Freeman's brief mention of humanizing antibodies not sufficient to enable the preparation of such humanized antibodies, and that consequently, Freeman can not serve as an anticipatory reference.

Applicants also note that is not always simple to prepare an antigen binding properties comparable to those of the starting murine antibody. For example, Queen *et al.* teaches that the CDR grafted antibodies taught therein have approximately one third the binding activity of the starting murine antibodies (P.N.A.S. 86:10029 (1989), Abstract; a copy of the reference was filed with the Information Disclosure Statement filed July 27, 2000). Co *et al.* (P.N.A.S. 88:2869, 2869 (1991); a copy is enclosed with the concurrently filed Information Disclosure Statement) teach that:

> generation of other fully humanized antibodies has proved unexpectedly difficult because significant loss of binding affinity generally resulted from simple grafting or hypervariable regions, probably due to distortion of the complementarity-determining region (CDR) conformation by the human framework.

Other references also teach that CDR replacement into human framework regions can lead to a significant loss of binding affinity to the antigen (*See, e.g.*, Tempest *et al.*,

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Biotechnology, 9:266 (1992) and Shalaby *et al.*, J. Exp. Med. 17:217 (1992), enclosed with the concurrently filed Information Disclosure Statement).

As mentioned above, claims 1-3, as amended, recite the limitation that the humanized immunoglobulin "has a binding affinity of at least about 10^7 M^{-1}". All other claims are dependent on claims 1-3. This limitation is supported in the specification, which shows that the invention encompasses antibodies with a binding affinity of at least about 10^7 M^{-1} (specification at page 10, line 13). The specification also shows that humanized antibodies are based on the murine 3D1 antibody which has a comparable binding affinity to the murine antibody (see Example 3). More specifically, results showed that both humanized IgG4 and humanized IgG2.M3 anti-B7-2 antibodies have a similar high binding affinity as the murine 3D1 antibody, indicating no loss of affinity for B7-2 with these particular humanizations of the 3D1 antibody (see Figure 3). Maintaining such high affinity, without loss due to the humanization process was very surprising. Thus, in contrast to Freeman, and despite the difficulty of such an undertaking, Applicants provide and claim an inventive, enabled invention which comprises successfully humanizing individual antibodies without loss of binding affinity.

For all of these reasons, Applicants submit that the rejection under 35 U.S.C. § 102(e) with regard to Freeman is improper, and ask that it be withdrawn.

B. Rejection under De Boer et al.

Claims 1-4 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by De Boer *et al.* (U.S. Patent No. 6,346,248; hereafter "De Boer"). Office Action at page 3. The Examiner alleges that De Boer teaches the use of B7-2 specific immunotoxins,

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including recombinant antibodies thereof in order to cause immunosuppression and thus to inhibit transplant rejection. The Examiner alleges that the use of the antibodies taught by De Boer inherently anticipates the instant claimed invention. Applicants traverse.

To anticipate the claimed invention, the reference must contain all of the claim limitations. M.P.E.P. § 2131. Claims 1-3 have been amended to recite methods of administering an immunoglobulin to a patient, wherein the immunoglobulin comprises "at least a portion of an immunoglobulin of human origin derived from the III2R and/or the H2F antibody". Claims 1-3, as amended, also recite the limitation that the humanized immunoglobulin "has a binding affinity of at least about 10^7 M^{-1}". All other claims depend on claims 1-3 and are thereby encompassed by these amendments. Although De Boer discloses that immunotoxins may comprise humanized antibodies raised against B7-2 (CD-86) (DeBoer, Abstract), the reference does not disclose that portions of the humanized immunoglobulin may be derived from the III2R and/or the H2F antibody and does not discuss the binding affinity of any humanized antibodies. Because De Boer does not disclose all of the limitation set out in the claims, Applicants submit that De Boer can not serve as an anticipatory reference.

Additionally, De Boer did not make any humanized antibodies, but only briefly mentioned that the antibodies of the invention can be humanized (column 7, lines 42-48). As discussed above, Applicants provide and claim an inventive, enabled invention which comprises successfully humanizing individual antibodies without loss of binding affinity. This was done despite the difficulty of raising such antibodies. Applicants

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submit that De Boer's brief mention of humanizing antibodies not sufficient to enable the preparation of such humanized antibodies, which is as required to show anticipation.

For all of these reasons, Applicants submit that the rejection under 35 U.S.C. § 102(e) with regard to De Boer is improper, and ask that it be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this Application and the timely allowance of the pending claims.

Please charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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APPENDIX OF AMENDMENTS

Paragraph at page 2, beginning at line 24:

The invention also embodies a humanized immunoglobulin having a binding specificity for B7-2 comprising a heavy chain and/or a light chain. The light chain comprises a CDR (e.g., CDRI, CDR2 and CDR3) derived from an antibody of nonhuman origin which binds B7-2 and a FR derived from a light chain of human origin (e.g., H2F antibody). The heavy chain comprises a CDR (e.g.,CDRI, CDR2 and CDR3) derived from an antibody of nonhuman origin which binds B7-2 and a FR region derived from a heavy chain of human origin (e.g., the human [I2R] III2R antibody). The immunoglobulin can further comprise CDR1, CDR2 and CDR3 for the light or heavy chain having the amino acid sequence set forth herein or an amino acid.

Paragraph at page 3, beginning at line 21:

Another embodiment of the invention is a humanized immunoglobulin heavy chain that is specific for B7-2 and comprises CDRI, CDR2 and/or CDR3 of the heavy chain of the 3D1 antibody, and a human heavy chain FR (e.g., [I2R] III2R antibody). The invention pertains to a humanized immunoglobulin heavy chain that comprises a variable region shown in Figure 2A (SEQ ID NO: 6). The invention also pertains to an isolated nucleic acid sequence that encodes a humanized variable heavy chain specific for B7-2 that comprises a nucleic acid, such as the sequence shown in Figure 2A (SEQ

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ID NO: 5), a nucleic acid that encodes the amino acid sequence shown in Figure 2A (SEQ ID N0: 6), a nucleic acid which hybridizes thereto under stringent hybridization conditions, and a nucleic acid which is the complement thereof.

Paragraph at page 35, beginning at line 1:

To retain the binding affinity of the mouse antibody in the humanized antibody, the general procedures of Queen *et al.* were followed (Queen *et al. Proc. Natl. Acad Sci. USA* 86: 10029 (1989), U.S. Patent Nos. 5,585,089 and 5,693,762, the teachings of which are incorporated herein in their entirety). The choice of framework residues can be critical in retaining high binding affinity. In principle, a framework sequence from any human antibody can serve as the template for CDR grafting; however, it has been demonstrated that straight CDR replacement into such a framework can lead to significant loss of binding affinity to the antigen (Tempest *et al.*, *Biotechnology* 9: 266 (1992); Shalaby *et al.*, *J. Exp. Med.* 17: 217 (1992)). The more homologous a human antibody is to the original murine antibody, the less likely the human framework will introduce distortions into the mouse CDRs that could reduce affinity. Based on a sequence homology, [I2R] III2R was selected to provide the framework for the humanized 3D1 heavy chain and H2F for the humanized 3D1 light chain variable region. Manheimer-Lory, A. *et al.*, *J. Exp. Med.* 174(6):1639-52 (1991). Other highly homologous human antibody chains would also be suitable to provide the humanized antibody framework, especially kappa light chains from human subgroup 4 and heavy chains from human subgroup 1 as defined by Kabat.

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Paragraph at page 35, beginning at line 18:

Normally the heavy chain and light chain from the same human antibody are chosen to provide the framework sequences, so as to reduce the possibility of incompatibility in the assembling of the two chains. The [I2R] III2R antibody shows a high homology to the 3D1 heavy and light chains and thus, was chosen to provide the framework for the initial humanized antibody model. The 3D1 light chain variable region, however, shows a significantly higher homology to the H2F framework compared to any others, including [I2R] III2R. Therefore, H2F was chosen instead to provide the framework for the humanized 3D1 light chain variable region, while [I2R] III2R was selected to provide the framework for the heavy chain variable region.

Paragraph at page 36, beginning at line 1:

The computer programs ABMOD and ENCODE (Levitt *et al.*, *J. Mol. Biol.* 168: 595 (1983)) were used to construct a molecular model of the 3D1 variable domain, which was used to locate the amino acids in the 3D1 framework that are close enough to the CDRs to potentially interact with them. To design the humanized 3D1 heavy and light chain variable regions, the CDRs from the mouse 3D1 heavy chain were grafted into the framework regions of the human [I2R] III2R heavy chain and the CDRs from the mouse 3D1 light chain grafted into the framework regions of the human H2F light chain. At framework positions where the computer model suggested significant contact with the CDRs, the amino acids from the mouse antibody were substituted for the original

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human framework amino acids. For humanized 3D1, this was done at residues 27, 30, 48, 67, 68, 70 and 72 of the heavy chain and at residue 22 of the light chain. Furthermore, framework residues that occurred only rarely at their positions in the database of human antibodies were replaced by a human consensus amino acid at those positions. For humanized 3D1 this was done at residue 113 of the heavy chain and at residue 3 of the light chain.

Paragraph at page 37, beginning at line 12:

Likewise, many of the framework residues not in contact with the CDRs in the humanized 3D1 heavy and light chains can accommodate substitutions of amino acids from the corresponding positions of [I2R] III2R and H2F frameworks, from other human antibodies, from the mouse 3D1 antibody, or from other mouse antibodies, without significant loss of the affinity or non-immunogenicity of the humanized antibody. Table 2 lists a number of additional positions in the framework where alternative amino acids may be suitable.

1. (Amended) A method of inhibiting the interaction of a first cell bearing a B7-2 receptor with a second cell bearing B7-2, comprising contacting said [first] second cell with an effective amount of a humanized immunoglobulin having binding specificity for B7-2, said immunoglobulin comprising:

a) [an] at least one antigen binding region of nonhuman origin and

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b) at least a portion of an immunoglobulin of human origin derived from the III2R and/or the H2F antibody,

wherein the humanized immunoglobulin has a binding affinity of at least about 10^7 M^{-1}.

2. (Amended) A method of [modulating an immune response of a] inducing immunotolerance in a patient having a transplanted organ, tissue, cell, or the like comprising administering an effective amount of a humanized immunoglobulin having binding specificity for B7-2, said immunoglobulin comprising:

a) [an] at least one antigen binding region of nonhuman origin, and

b) at least a portion of an immunoglobulin of human origin derived from the III2R and/or the H2F antibody,

wherein the immunoglobulin is administered in a carrier, and wherein the humanized immunoglobulin has a binding affinity of at least about 10^7 M^{-1}.

3. (Amended) A method of [treating] reducing transplantation rejection in a patient having a transplanted organ, tissue, or cell, comprising administering a therapeutically effective amount of a humanized antibody having binding specificity for B7-2, said immunoglobulin comprising:

a) [an] at least one antigen binding region of nonhuman origin, and

b) at least a portion of an immunoglobulin of human origin derived from the III2R and/or the H2F antibody,

wherein the humanized immunoglobulin has a binding affinity of at least about 10^7 M^{-1}.

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